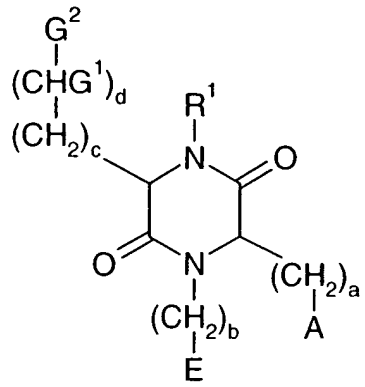
WHAT IS CLAIMED IS:

1. A compound of the formula:



Formula (I)

or an optical isomer, geometric isomer, diastereomer, tautomer, or a pharmaceutically acceptable salt thereof, wherein

A is $-NR^2R^3$ or guanidinyl, the last optionally substituted with C_{1-6}-alkyl, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

R^{11} and R^{12} independently of each other are hydrogen or C_{1-6}-alkyl;

Z^1 is C_{1-6}-alkylene;

e is an integer selected from 0 or 1;

R^{13} is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 is C_{1-6}-alkylene; and

R^{23} is aryl; and

R^{14} is hydrogen, C_{1-6}-alkyl, $-N(R^{15})(R^{16})$, C_{1-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, or C_{1-6}-alkoxy, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and

Z^2 is C_{1-6}-alkylene;

f is an integer selected from 0 or 1; and

R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

a is an integer selected from 1, 2, 3, 4, or 5;

E is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, -NR^4R^5, -CO-R^6, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and –L^1-Q^1, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, -CO-R^{24}, or aryl, wherein

R^{24} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^6 is C_{1-6}-alkyl or C_{1-6}-alkoxy;

L^1 is a direct bond, -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2- or –NR^{25}-, wherein

R^{25} is hydrogen or C_{1-6}-alkyl; and

Q^1 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -$NR^{26}R^{27}$, -CO-R^{28}, -$S(O)_2$-R^{29}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26} and R^{27} independently of each other are hydrogen, C_{1-6}-alkyl, or -CO-R^{30}, wherein

R^{30} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{28} is C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{29} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, or -$N(C_{1-6}$-alkyl$)_2$;

or

Q^1 is L^3-R^{31}, wherein

L^3 is -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2-, -CH_2-O-C(O)-, or -C(O)-O-CH_2-; and

R^{31} is aryl or heteroaryl;

b is an integer selected from 0, 1, or 2;

G^1 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cycloalkyl, C_{3-7}-cycloalkoxy, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^7R^8$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy, wherein

R^7 and R^8 independently of each other are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, $-CO-R^{32}$ or $-SO_2-R^{33}$, wherein

R^{32} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{33} is C_{1-6}-alkyl, $-NH-C_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$;

G^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$, wherein

R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, $-CO-R^{34}$ or $-SO_2-R^{35}$, wherein

R^{34} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{35} is C_{1-6}-alkyl, $-NH-C_{1-6}$-alkyl, or $-N(C_{1-6}\text{-alkyl})_2$;

L^2 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, $-O-CH_2-$ or $-NR^{36}-$, wherein

R^{36} is hydrogen or C_{1-6}-alkyl; and

Q^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37} and R^{38} independently of each other are hydrogen, C_{1-6}-alkyl or $-CO-R^{41}$, wherein

R^{41} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{39} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{40} is C_{1-6}-alkyl or trifluoromethyl;

c is an integer selected from 0, 1, or 2;

d is an integer selected from 0, or 1;and

R^1 is hydrogen, alkyl, alkenyl, or alkynyl.

2. The compound of claim 1, wherein A is $-NR^2R^3$.

3. The compound of claim 1, wherein R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)-N(R^{11})(R^{12})$,

$(Z^1)_e$-R^{13}, or -CO-R^{14}; and R^3 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}.

4. The compound of claim 1, wherein R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}.

5. The compound of claim 1, wherein R^{11} and R^{12} are hydrogen.

6. The compound of claim 1, wherein e is 1 and Z^1 is $-CH_2-$.

7. The compound of claim 1, wherein R^{13} is a cycloalkyl or aryl; either of which may be optionally substituted with C_{1-6}-alkyl, amino or -CO-O-Z^4-R^{23}.

8. The compound of claim 1, wherein R^{23} is C_{6-13}-aryl.

9. The compound of claim 1, wherein R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, or -CO-R^{14}.

10. The compound of claim 1, wherein R^{14} is hydrogen, C_{1-6}-alkyl, -$NR^{15}R^{16}$, C_{1-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{3-10}-heterocyclyl, $(Z^2)_f$-R^{21}, C_{5-14}-heteroaryl, or C_{1-6}-alkoxy.

11. The compound of claim 1, wherein R^{15} and R^{16} are each hydrogen.

12. The compound of claim 1, wherein R^{17} and R^{18} independently of each other are hydrogen, a C_{1-6}-alkylene-NH_2, or $(Z^3)_g$-R^{22}.

13. The compound of claim 1, wherein R^{22} is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl, or C_{5-14}-heteroaryl.

14. The compound of claim 1, wherein R^{17} and R^{18} are each hydrogen.

15. The compound of claim 1, wherein R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3, or C_{3-7}-cycloalkyl.

16. The compound of claim 1, wherein f is 1 and Z^2 is -CH_2-.

17. The compound of claim 1, wherein R^{21} is a heterocyclyl or heteroaryl.

18. The compound of claim 1, wherein A is guanidinyl optionally substituted with C_{1-6}-alkyl.

19. The compound of claim 1, wherein a is 1, 4, or 5.

20. The compound of claim 1, wherein A is $-NR^2R^3$, R^2 and R^3 are hydrogen, and a is 4 or 5.

21. The compound of claim 1, wherein the sum of the carbon and nitrogen atoms in the -$(CH_2)_a$-A group is at least 4.

22. The compound of claim 1, wherein R^2 is C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, C_{3-6}-alkylene-CN, C_{3-6}-alkylene-OH, C_{3-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}; and R^3 is C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}; R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -$N(R^{42})(R^{43})$, R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl; R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}); Z^3 is C_{1-6}-alkylene; g is an integer selected from 0 or 1; R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl; R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; Z^2 is C_{1-6}-alkylene; f is an integer selected from 0 or 1; R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

23. The compound of claim 1, wherein R^2 and R^3 independently of each other are C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}; R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -$N(R^{42})(R^{43})$; R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl; R^{17} and R^{18}

independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}); Z^3 is C_{1-6}-alkylene; g is an integer selected from 0 or 1; R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl; R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; Z^2 is C_{1-6}-alkylene; f is an integer selected from 0 or 1; R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

24. The compound of claim 1, wherein R^2 and R^3 independently of each other are C_{3-6}-alkyl, C_{3-6}-alkylene-CN, C_{3-6}-alkylene-OH, C_{3-6}-alkylene-C(O)-NH_2, $(Z^1)_e$-R^{13}, or -CO-R^{14}; R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-N(R^{15})(R^{16}), C(R^{17})(R^{18})-N(R^{19})(R^{20}), heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -N(R^{42})(R^{43}); R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl; R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}); Z^3 is C_{1-6}-alkylene; g is an integer selected from 0 or 1; R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl; R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; Z^2 is C_{1-6}-alkylene; f is an integer selected from 0 or 1; R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

25. The compound of claim 1, wherein E is aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, -NR^4R^5, -CO-R^6, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and –L^1-Q^1.

26. The compound of claim 1, wherein L^1 is a direct bond, -CH_2-, or -O.

27. The compound of claim 1, wherein Q^1 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl, or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -$NR^{26}R^{27}$, -CO-R^{28}, -$S(O)_2$-R^{29}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy.

28. The compound of claim 1, wherein R^{26} and R^{27} independently of each other are hydrogen or C_{1-6}-alkyl.

29. The compound of claim 1, wherein R^{28} is methyl.

30. The compound of claim 1, wherein R^{29} is C_{1-6}-alkyl.

31. The compound of claim 1, wherein R^{31} is C_{6-13}-aryl or C_{3-10}-heteroaryl.

32. The compound of claim 1, wherein (a) b is 1, (b) c is 1, and/or (c) d is 0.

33. The compound of claim 1, wherein G^2 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$.

34. The compound of claim 1, wherein R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, C_{6-13}-aryl, C_{5-14}-heteroaryl, $-CO-R^{34}$ or $-SO_2-R^{35}$.

35. The compound of claim 1, wherein L^2 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, or $-O-CH_2-$.

36. The compound of claim 1, wherein Q^2 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl, or C_{3-7}-cycloalkoxy.

37. The compound of claim 1, wherein R^{37} and R^{38} independently of each other are hydrogen or C_{1-6}-alkyl.

38. The compound of claim 1, wherein R^{39} is hydrogen or C_{1-6}-alkyl.

39. The compound of claim 1, wherein R^{40} is trifluoromethyl.

40. The compound of claim 1, wherein R^1 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl.

41. The compound of claim 1, where the compound is selected from the group consisting of

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-1-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-benzyloxy-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(S,S)-6-(4-amino-butyl)-1,3-bis-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-benzo[b]thiophen-3-ylmethyl-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-benzoyl-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(4'-methoxy-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(4'-chloro-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(9*H*-fluoren-2-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-4'-[2-(4-amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carboxylic acid methyl,

(*S,S*)-6-(4-amino-butyl)-3-(4-benzoyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-chloro-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-methyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-4'-[2-(4-amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile,

(*S,S*)-6-(4-amino-butyl)-1-(4-cyclohexyloxy-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-[4-(3-trifluoromethyl-cyclohexyloxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(4-cyclohexyl-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-methylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-propoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-isopropoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-pyrrol-1-yl-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclopropylmethoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclohexyloxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-isopropylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-m-tolyloxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-methoxy-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-[4-(4-dimethylamino-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-[4-(4-methoxy-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-1-[4-(3-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-[4-(4-ethanesulfonyl-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-chloro-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-3-[4-(4-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S,S*)-3-[4-(3-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-methoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-ethoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-trifluoromethoxy-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-fluoro-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-nitro-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(pyridin-3-yloxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-dimethylamino-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(6-phenyl-pyridin-3-ylmethyl)-piperazine-2,5-dione,

(*S,S*)-3-{4-[5-(4-amino-butyl)-4-biphenyl-4-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl]-phenoxy}-benzaldehyde,

(*S,S*)-6-(4-amino-butyl)-1-(4-bromo-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-isopropoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-[4-(2-amino-ethylamino)-butyl]-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide,

(*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-*N*-pyridin-4-ylmethyl-propionamide,

(*S,S)*-3-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-*N*-piperidin-4-ylmethyl-butyramide,

(*S,S*)-3-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-*N*-piperidin-4-ylmethyl-propionamide,

(*S,S*)-6-{[bis-(3*H*-imidazol-4-ylmethyl)-amino]-methyl}-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-amino-*N*-(2-amino-2-methyl-propyl)-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-butyramide,

(*S,S*)-1-[4-(4-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-hydroxymethyl-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-{4-[(1*H*-imidazol-2-ylmethyl)-amino]-butyl}-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-6-{4-[(pyridin-2-ylmethyl)-amino]-butyl}-piperazine-2,5-dione,

(*2R,2'S,5'S*)-2-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-(1*H*-imidazol-4-yl)-propionamide,

(*S,S*)-2-(3-amino-propylamino)-*N*-[1-[4-(methyl-phenyl-amino)-benzyl]-3,6-dioxo-5-(4-propoxy-benzyl)-piperazin-2-ylmethyl]-acetamide,

N-[4-((2S,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-acetamide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

N-[4-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-guanidine hydrochloride,

(3*S*,6*S*)-6-[4-(3-amino-pyridin-2-ylamino)-butyl]-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

{4-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-yl]-butylamino}-acetonitrile,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-acetamide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-[(cyclohexylmethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-[(ethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-4-ylmethyl-amino)-methyl]-piperazine-2,5-dione,

3-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-propionamide,

4-{[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-(piperidine-4-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester,

4-{[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-((*R*,*S*)-piperidine-3-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester,

piperidine-4-carboxylic acid ((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide,

(*R*,*S*)-piperidine-3-carboxylic acid ((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide,

4-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-butyramide,

(3*S*,6*S*)-6-{[(3-amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

1H-imidazole-4-carboxylic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

2-amino-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-acetamide,

3-amino-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide,

N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-2-piperidin-4-yl-N-piperidin-4-ylmethyl-acetamide,

(*R*,*S*)-2,5-diamino-pentanoic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

(3*S*,6*S*)-6-{[(3-dimethylamino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

3-amino-N-(1-methyl-piperidin-4-ylmethyl)-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-propionamide,

piperidine-3-carboxylic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-{[bis-(1-methyl-piperidin-4-ylmethyl)-amino]-methyl}-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-6-{[(3-amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,

(3*S*,6*S*)-6-{[(3-hydroxy-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,

3-amino-N-[(2*S*,5*S*)-3,6-dioxo-1-(4-phenoxy-benzyl)-5-(4-trifluoromethyl-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-(*R*,*S*)-morpholin-2-yl-N-piperidin-4-ylmethyl-acetamide,
(3*S*,6*S*)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-piperazine-2,5-dione,
(3*S*,6*S*)-1-(4-phenoxy-benzyl)-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-cyclopropylamino-N-piperidin-4-ylmethyl-acetamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-(2,2,2-trifluoro-ethylamino)-acetamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-imidazol-1-yl-N-piperidin-4-ylmethyl-acetamide,
2-[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amino]-acetamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyridin-3-yl-acetamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-nicotinamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyrrolidin-1-yl-acetamide,
3-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-pyridin-3-ylmethyl-propionamide,
(*S*,*S*)-6-(4-Amino-butyl)-3-(3-chloro-4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S*,*S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(1-methoxy-naphthalen-2-ylmethyl)-piperazine-2,5-dione,
(*S*,*S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(6-chloro-naphthalen-2-ylmethyl)-piperazine-2,5-dione,
(*S*,S)-6-(4-Amino-butyl)-3-(4-amino-3,5-dibromo-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-(4-hydroxy-3,5-dibromo-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-[4-(pyridin-4-yloxy)-benzyl]-piperazine-2,5-dione,

(*S,S)*-6-(4-Amino-butyl)-1-(4-phenoxy-benzyl)-3-(5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-(4-*o*-tolyloxy-benzyl)-piperazine-2,5-dione,

(*S,S)*-6-(4-Amino-butyl)-1-[4-(3-chloro-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(3-methoxy-naphthalen-2-ylmethyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-1-[4-(tert-butyl-diphenyl-silanyloxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (exp 15)

(*S*,S)-Carbonic acid 4-[2-(4-amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-phenyl ester benzyl ester,

(*S*,S)-6-(4-Amino-butyl)-1-[4-(methyl-phenyl-amino)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-1-(4-benzyl-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-1-(3-methyl-4-phenoxy-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-1-(3-methoxy-4-phenoxy-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-3-(4-Amino-butyl)-4-biphenyl-4-ylmethyl-1-methyl-6-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(5-Amino-pentyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-(3-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-(4-benzyloxy-benzyl)-1-(3-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-naphthalen-1-ylmethyl-1-(3-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-biphenyl-4-ylmethyl-1-(3-phenoxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(5-Amino-pentyl)-3-(4-benzyloxy-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(5-Amino-pentyl)-1,3-bis-(4-benzyloxy-benzyl)-piperazine-2,5-dione,

(*S*,S)-6-(5-Amino-pentyl)-1-(4-benzyloxy-benzyl)-3-naphthalen-1-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(5-Amino-pentyl)-1-(4-benzyloxy-benzyl)-3-biphenyl-4-ylmethyl-piperazine-2,5-dione,

(*S*,S)-6-(4-Amino-butyl)-3-(3,4-dichloro-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione, (*S*,S)-6-(4-Amino-butyl)-3-naphthalen-1-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione, (*S*,S)-6-(4-Amino-butyl)-1-(9*H*-fluoren-3-ylmethyl)-3-naphthalen-1-ylmethyl-piperazine-2,5-dione, (*S*,S)-6-(4-Amino-butyl)-1-(4-benzyloxy-benzyl)-3-naphthalen-1-ylmethyl-piperazine-2,5-dione, and a combination of any thereof.

42. A composition comprising the compound of claim 1 in an amount sufficient to induce a physiological response in a subject associated with the modulation of melanocortin receptor activity and a pharmaceutically acceptable carrier, diluent, or excipient.

43. A method for modulating melanocortin receptor activity in a subject comprising administering to the subject the composition of claim 42 in an amount sufficient to detectably modulate melanocortin receptor activity.

44. The method of claim 43, wherein administration of the composition detectably modulates MC4 receptor activity.

45. The method of claim 44, wherein administration of the composition also detectably modulates MC3 receptor activity.

46. The method of claim 43, wherein administration of the composition detectably modulates MC5 receptor activity.

47. The method of claim 46, wherein administration of the composition also detectably modulates MC3 receptor activity.

48. A method of regulating exocrine gland secretion, regulating aldosterone secretion, suppressing stress-induced alarm substances, stimulating an exocrine gland function, stimulating cardiac function, stimulating testicular function, or any combination thereof in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

49. A method of inducing, enhancing, and/or promoting the treatment or prevention of hypertension in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

50. A method of increasing antipyretic activity in a subject comprising administering a therapeutically effective amount of the composition of the compositon of claim 42 to the subject.

51. A method for inducing, enhancing, and/or promoting lipolysis in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

52. A method for promoting the suppression of appetite, inducing satiety, or a combination thereof in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

53. A method of reducing the risk, onset, and/or severity or promoting the treatment of at least one condition associated with the activation of the MC4 receptor in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

54. The method of claim 53, wherein the at least one condition comprises hyperglycemia, impaired glucose tolerance, diabetes, dyslipidemia, hyperlipidemia, or a combination of any thereof.

55. A method of reducing the risk, onset, and/or severity or promoting the treatment of at least one condition associated with the activation of the MC1 receptor in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

56. The method of claim 55, wherein administration of the composition detectably increases the subject's skin pigmentation, modulates an inflammatory response in the skin of the subject, reduces or prvents contact dermatitis in the subject, modulates an immune response in

the subject, at least partially inhibits a chronic inflammatory response in the subject, or induces, promotes, and/or enhances any combination thereof.

57. A method of reducing the risk, onset, and/or severity or promoting the treatment of at least one condition associated with the activation of the MC2 receptor in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

58. A method of regulating glucocorticoid production in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

59. A method of reducing the risk, onset, and/or severity or promoting the treatment of at least one condition associated with the activation of the MC3 receptor in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

60. The method of claim 59, wherein the condition is hypertension, obesity, sexual dysfunction, or a combination of any thereof.

61. A method of reducing blood pressure; reducing heart rate; inducing, enhancing and/or promoting natriuresis; or inducing, promoting, and/or enhancing any combination thereof in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.

62. A method of reducing the risk, onset, and/or severity or promoting the treatment of at least one condition associated with the activation of the MC5 receptor in a subject comprising administering a therapeutically effective amount of the composition of claim 42 to the subject.